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(54) Title of invention    Medical Hydrogel  
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## **PATENT SPECIFICATION**

### **1. TITLE OF THE INVENTION**

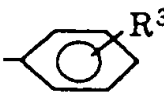
Medical hydrogel

### **2. CLAIM**

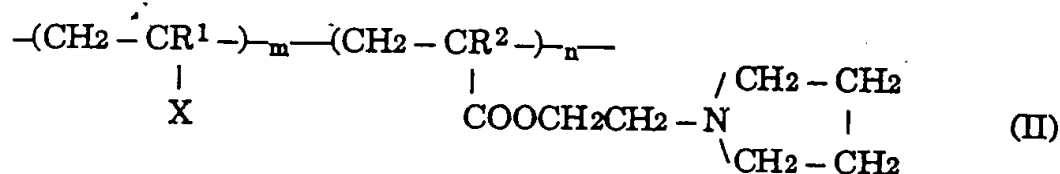
(1) Medical hydrogel which is obtained by making N-2-methacryloyl oxyethyl-2-pyrrolidone and/or N-2-acryloyl oxyethyl-2-pyrrolidone to be insoluble in water by physical means and/or copolymerization with organic monomers which do not contain metal.


(2) Medical hydrogel which is described in the CLAIM (1) and its organic monomer is represented by the following general formula I;



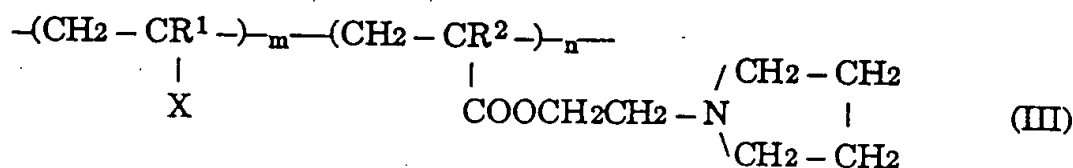
[R<sup>1</sup> is hydrogen or methyl group, X is  (R<sup>3</sup> is an alkyl group with carbon number 1 to 4, or halogen), -CN, -Cl or -COOR<sup>4</sup> (R<sup>4</sup> is an alkyl group with carbon number 1 to 16, a group made by hydrogen of the alkyl group being substituted with ester residue having double bond, a phenyl group or a phenylene group)].

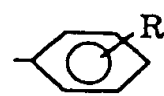
(3) Medical hydrogel which is described in the CLAIM (1) or (2) which is represented by following general formula II;



[in the formula, R<sup>1</sup> and R<sup>2</sup> are hydrogen or methyl group, X is  (R<sup>3</sup> is an alkyl group with carbon number 1 to 4, or halogen) or -COOR<sup>4</sup> (R<sup>4</sup> is an alkyl group with carbon number 1 to 16, a phenyl group or a phenylene group), and 2/8 < m/n < 7/3].

(4) Medical hydrogel which is described in the CLAIM (1) or (2) and which is added with water resistance by one of the means of physical means such as gamma ray irradiation or electron beam irradiation, copolymerization with multi-functional crosslinking monomer, or surface grafting reaction by such as plasma method, to copolymer or single polymer which is represented by the following general formula III;



[in the formula, R<sup>1</sup> and R<sup>2</sup> are hydrogen or methyl group, X is  (R<sup>3</sup> is an alkyl group with carbon number 1 to 4, or halogen) or -COOR<sup>4</sup> (R<sup>4</sup> is an alkyl group with carbon number 1 to 16, a phenyl group or a phenylene group), and m/n ≤ 2/8].

(5) Medical hydrogel which is described in the CLAIM (3) and the X in the general formula II is -COOR<sup>4</sup> (in the formula, R<sup>4</sup> is an alkyl group, phenyl group or a phenylene group with carbon number 1 to 16).

(6) Medical hydrogel which is described in the CLAIM (4) and the X in the general formula III is  $-\text{COOR}^4$  (in the formula,  $\text{R}^4$  is an alkyl group, phenyl group or a phenylene group with carbon number 1 to 16).

### 3. DETAILED DESCRIPTION OF THE INVENTION

#### (Application field in the industry)

This invention concerns medical hydrogel which is excellent in bio-compatibility. In detail, it concerns medical hydrogel which is excellent in bio-compatibility and is able to be used for such as thermal reactive gel, contact lenses, artificial lenses, artificial blood vessel, artificial skin, anti-thrombusic material, and modification of surface of medical substrate to be hydrophilic.

#### (Prior technologies)

Previously, as for the materials to be used for medical hydrogel, following ones have been known; cellulose, collagen, gelatin, polyvinyl alcohol and acrylic materials which are hydroxy-alkyl (meth)acrylate polymers represented by poly-2-hydroxyethyl (meth)acrylate, and acrylamide polymers such as n-isopropyl (meth)acrylamide, N-n-propyl acrylamide and N,N-dimethyl acrylamide (such as Patent publication (Kokai) Shou 58-174,408, Patent publication (Kokai) Shou 58-179,256, Patent publication (Kokai) Hei 1-129,008). However these are not sufficient in the bio-compatibility.

On the other hand, as for the polymers having pyrrolidone ring, poly(N-vinyl pyrrolidone) and copolymers and blend materials with these have been known (such as Patent publication (Kokai) Shou 51-55,351), however, the copolymers of N-vinyl pyrrolidone monomer are not sufficient in bio-compatibility and satisfactory hydrogel has not been obtained yet.

As for the N-2-methacryloyl oxyethyl-2-pyrrolidone polymer being used in this invention, such as copolymer with silicone (WO82/03397), copolymer with 1,3-butadiene (West Germany Patent laid open 2,048,312), and copolymer with 1-eicosene (Great Britain Patent 1,101,163) have been known. However, satisfactory bio-compatibility have not been yet obtained with these copolymers either.

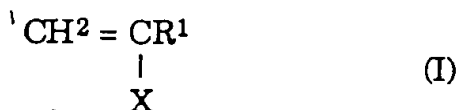
#### (The problems that the invention is to solve)


Accordingly, the objective of this invention is to provide medical hydrogel with excellent bio-compatibility.

(Means to solve the problems)

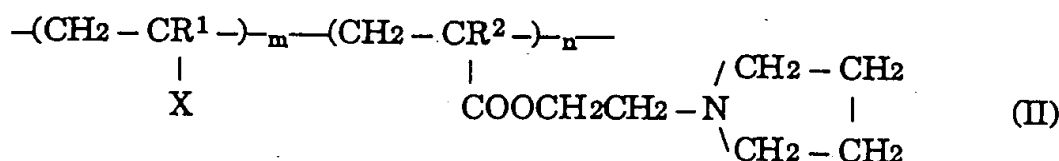
These objectives are accomplished by medical hydrogel which is obtained by making N-2-methacryloyl oxyethyl-2-pyrrolidone and/or N-2-acryloyl oxyethyl-2-pyrrolidone to be insoluble in water by physical means and/or copolymerization with organic monomers which do not contain metal.

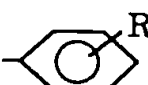
This invention is also medical hydrogel of which organic monomer is described by the following general formula I;



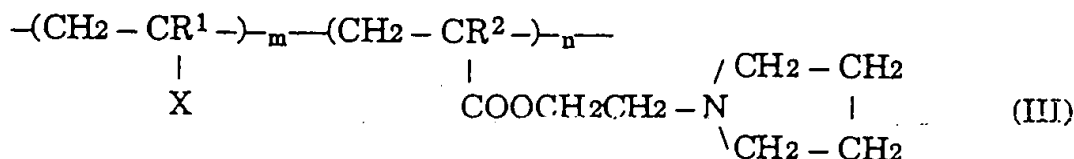
[R<sup>1</sup> is hydrogen or methyl group, X is  (R<sup>3</sup> is an alkyl group with carbon number 1 to 4, or halogen), -CN, -Cl or -COOR<sup>4</sup> (R<sup>4</sup> is an alkyl group with carbon number 1 to 16, a group made by hydrogen of the alkyl group being substituted with ester residue having double bond, a phenyl group or a phenylene group].

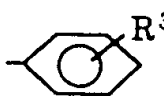
Further, this invention is medical hydrogel which is represented by following general formula II;



[in the formula, R<sup>1</sup> and R<sup>2</sup> are hydrogen or methyl group, X is  (R<sup>3</sup> is an alkyl group with carbon number 1 to 4, or halogen) or -COOR<sup>4</sup> (R<sup>4</sup> is an alkyl group with carbon number 1 to 16, a phenyl group or a phenylene group), and 2/8 < m/n < 7/3].

This invention is also medical hydrogel which is added with water resistance by one of the means of physical means such as gamma ray irradiation or electron beam irradiation, copolymerization with multi-functional crosslinking monomer, or surface grafting reaction by such as plasma method, to copolymer of single polymer which is represented by the following general formula III;



[in the formula,  $R^1$  and  $R^2$  are hydrogen or methyl group, X is  ( $R^3$  is an alkyl group with carbon number 1 to 4, or halogen) or  $-\text{COOR}^4$  ( $R^4$  is an alkyl group with carbon number 1 to 16, a phenyl group or a phenylene group), and  $m/n \leq 2/8$ ]. This invention is further medical hydrogel of which X in the general formula II is  $-\text{COOR}^4$  (in the formula,  $R^4$  is an alkyl group, phenyl group or a phenylene group with carbon number 1 to 16).

This invention is also medical hydrogel of which X in the general formula III is  $-\text{COOR}^4$  (in the formula,  $R^4$  is an alkyl group, phenyl group or a phenylene group with carbon number 1 to 16).

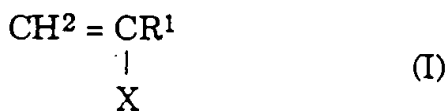
### (Functions)

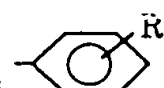
The medical hydrogel which is excellent in bio-compatibility is provided by making N-2-(meth)acryloyl oxyethyl-2-pyrrolodone to be insoluble in water by physical means and/or copolymerization with organic monomers which do not contain metals as above described. Especially it is composed by crosslinking to make water insoluble or graft reacting the random copolymer or the single polymer described by the said general formula II or III.

The composition ratio of the random copolymer is preferred to be  $2/8 < m/n < 7/3$ . Because if m is excessive at  $m/n \geq 7/3$ , the hydrophilicity will be reduced to lower the bio-compatibility, and on the other hand if  $m/n \leq 2/8$ , obtained copolymer or single polymer will be water soluble. Accordingly, if  $m/n \leq 2/8$ , it is essential to use it after making it insoluble by physical means, copolymerization with multi-functional cross linking monomer, or graft reacting with hydrophobic monomer.

The water insoluble and not cross linked hydrogel of  $2/8 < m/n < 7/3$  that obtained by this invention is soluble in such as chloroform, dimethyl formaldehyde, acetone, tetrahydrofuran and ethyl acetate, however, it is not soluble in such as water, n-hexane and ether. Also, obtained hydrogel is very good in bio-compatibility because its cell toxicity is low.

These hydrogels are obtained by copolymerizing monomer which is represented by a general formula I;



[ $R^1$  is hydrogen or methyl group, X is  ( $R^3$  is an alkyl group with carbon

number 1 to 4, or halogen),  $-\text{CN}$ ,  $-\text{Cl}$  or  $-\text{COOR}^4$  ( $\text{R}^4$  is an alkyl group with carbon number 1 to 16, a group made by hydrogen of the alkyl group being substituted with ester residue having double bond, a phenyl group or a phenylene group], especially (meth)acrylate with X being  $-\text{COOR}^4$  ( $\text{R}^4$  is as described above), and N-2-(methacryloyl oxyethyl-2-pyrrolidone in a mole ratio exceeding 2/8 but less than 7/3, for example. The reaction is conducted under the existence or without the existence of organic solvent, using radical polymerization initiator, under a temperature at 20 to 100 °C, preferably at 30 to 80 °C for 1 to 20 hours, preferably for 2 to 10 hours. Normally it is preferable to conduct the reaction in organic solvent. As for the organic solvent, there are such as chloroform, dimethyl-formaldehyde and acetone. As for the polymerization initiator, there are such as azobis-isobutyl-nitrile, lauloyl peroxide, benzoyl peroxide, dicumyl peroxide and di-isopropyl peroxy-dicarbonate.

### (Examples)

In the followings, this invention is further explained in detail by using examples. Examples 1-9

Monomers of which compositions are shown in the Table 1 and azobis-isobutyl-nitril of 0.5 mole % concentration were dissolved in 10 ml of chloroform and after purging with nitrogen, polymerization was done in sealed glass tube at 60 °C for 3 to 5 hours. After opening the tube, it was re-precipitated with ether to obtain polymer. The composition of the copolymers (hydrogel) was determined by element analysis and infrared absorption spectrum. The results are shown in the Table 1.

Table 1

Examples	charged mole ratio	MMA (g)	MAOEPD (g)	yield (g)	MMA/MAOEPD in co-polymer (mole ratio)	water content in co-polymer (weight %)	contact angle (°C)*
1	9/1	1.64	0.36	0.68	18/22	5	55
2	7/3	1.08	0.92	0.89	71/29 <sup>1)</sup>	17	46
3	6/4	0.86	1.14	1.01	59/41	28	35
4	5/5	0.69	1.33	0.98	49/51 <sup>2)</sup>	36	33
5	4/6	0.50	1.50	0.76	40/60	74	28
6	3/7	0.63	1.64	0.98	29/71 <sup>3)</sup>	85	23
7	2/8	0.17	1.33	0.47	28/72	dissolved	-
8	1/9	0.08	1.42	0.66	10/90	dissolved	-
9	0/10	0	1.50	0.37	0/100	dissolved	-

\*Translator's note: This [°C] should be a mistake of [°] (degree).

charged mole ratio: MMA/MAOEPD

MMA: methyl methacrylate

1) nitrogen content 3.12 %

2) nitrogen content 4.60 %

3) nitrogen content 5.96 %

The chloroform solutions of the said Examples 1-6 (concentration: 10 weight percent) were coated on plastic sheets for tissue culture (made by Wako Junyaku Co., Ltd.), dried sheets were placed in laboratory dishes, and cell suspending solution (epithelial cell strain from human gingiva Ca. 9. 22) containing 20 % calf serum was applied on them, then the laboratory dishes were sealed with poly-tetra-fluoro-ethylene tape and cultured in a constant temperature chamber at 37 °C. They were recorded by a VCR at a rate of 0.1 second for every 30 seconds. The VCR was played back after cultivating for 3 to 7 days to observe the situation of the cells. The results showed that all of them were bio-compatible.

#### (Effect of the invention)

As above described, because this invention is the medical hydrogel which is obtained by making N-2-(meth)acryloyl oxyethyl-2-pyrrolidone to be insoluble in water by the physical means and/or the copolymerization with organic monomer which does not contain metal, this invention is good in attachment property of cells and good in bio-compatibility, and further because of the pyrrolidone ring as the pendant group, it is excellent in mutual effect with several iodine and phenolic medicines, therefore, is very useful as the medical material.

Assignee: Terumo Corp.

Attorney Patent attorney: Hatta, Mikio

*Translated by: Hideyo Sugimura 490-0233, March 27, 1998*